REMARKS

This is response to the non-final Office action (Paper No. 20080326) mailed 4 April 2008.

Claims 1, 5-9, and 21-30 are pending in this application.

Claims 1, 21-22, 27 and 30 have been amended and claims 23 and 24 have been canceled without disclaiming their subject matter.

No new matter has been added.

I. Claim Rejections – 35 USC §103

A. Claim(s) 1, 7, 8, 21, 22, 25 and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. (J Forensic Sci. 2002 May;47(3):589-92) in view of Palmirotta et al. (Journal of Forensic Science. March 1998. (43) 2, 431-434), in further view of Jurka (Nucleic Acids Research. 1993. Vol. 21. No. 9, 2252) as evidenced by Batzer et al. (Journal of Molecular Evolution. 1996. 42, 3-6).

The examiner failed to establish the *prima facie* case of obviousness for the following reasons.

1. There is no reasonable expectation of success in designing primers for the intra-*Alu* polymerase chain reaction amplification of an Alu element being more enriched in the human genome than in any non-human primate genome or present only in the human genome in order to achieve the same as or similar or better results to the Sifis et al.

There must be a reasonable expectation of success, based on at least some degree of predictability, at the time the invention was made. In the case of *Amgen , Inc. v. Chugai pharmaceutical Co.*, 927 F.2d 1200, 1207-08 (Fed. Cir.). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 1 recites "said Alu element being more enriched in the human genome than in any non-human primate genome", claim 21 recites "said Alu element being present only in the human genome", and claim 22 recites "a copy number of said predetermined genomic DNA in the human genome being higher than a copy number of said predetermined genomic DNA in any non-human primate genome".

In the Office action, the examiner responded that:
"first, it is noted that the references provide evidence of the "preferable" content of PCR primers and not the absolute requirements (i.e., the references do not teach that Alu

sequences, such as those having a GC content of greater than 60%, can never be amplified. Applicant is further reminded that obviousness does not require absolute predictability (see MPEP 2143.02). Applicant has provided no evidence that Alu sequences occurring exclusively in humans, such as those provided by Jurka, differ in structure to such a degree that would have indicated to a skilled person that such sequences were absolutely incapable of being amplified. "

The examiner's arguments are not proper.

The applicant did not argue that absolute predictability is required. The examiner did argue that only when such sequences were absolutely incapable of being amplified, there is no reasonable expectation of success.

"A reasonable likelihood of success does not necessarily mean an absolute predictability, but rather a reasonable expectation of success. *Yamanouchi Pharm. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000). That is, what obviousness requires is "a REASONABLE expectation of success", neither absolute predictability, not very low chance of success.

As stated in the previous response, the applicant showed that "Fine-tuning of PCR conditions is not practicable for all target sequences whenever a large number of genes of different lengths and GC content are to be amplified in parallel." (See Benita et al., Nucleic Acid Research, Vol.31 No. 16, abstract, which is attached hereto as Appendix I.) "[I]t is known that DNA template with a very high or very low GC/AT ratio can be difficult to amplify." (See *Id* at col. 2.) "Most Alu elements located in the primate genomes that have been sequenced (e.g., human, chimpanzee, and rhesus macque) exist in high-GC content regions [3-5] and also have high GC content (an average of ~62.7%)", citing Quentin Y, Nucleic Acid Res. 20: 487-493. (See Han et al., PLOS genetics, vol. 3, p 1939-1949, 1943, which is attached hereto as Appendix II..)

Even if the examiner argued that Sifis provides evidence that core Alu sequences may be amplified through an intra-Alu PCR procedure, Sifis does not show that there is reasonable expectation of success in overcoming two obstacles, (1) the need to incorporate subfamily specific diagnostic mutations into the primer design, and (2) the high intrinsic GC content of *Alu* repeats. (The instant application specifically recognizes that "The need to incorporate subfamily specific diagnostic mutations into the primer design, as well as the high intrinsic GC content of *Alu* repeats, made it challenging to identify oligonucleotide primers acceptable to the design software packages.") That is, in addition to the high GC content, the need to incorporate subfamily specific diagnostic mutations into the primer design makes it much more difficult to design primers acceptable to quantitate human DNA.

That is, in view of evidence, there is no reasonable expectation of success that primers for the intra-Alu polymerase chain reaction amplification to quantitate a human DNA can be designed.

2. The examiner failed to show that there is some teaching, suggestion, or motivation to modify or combine the references.

Claims 23 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis *et al.* in view of Palmirotta *et al.*, in further view of Jurka as applied to claim 1 above, and in further view of Fortina *et al.* ("Non-radioactive detection of the most common mutations in the cystic fibrosis transmembrane conductance regulator gene by multiplex allele-specific polymerase chain reaction" Hum Genet. 1992 Dec; 90(4): 375-8).

The features of claims 23 and 24 have been incorporated into claims 1 and 21, respectively.

Therefore, the following response is applied to the patentability of claims 1 and 21 as amended.

In the Office action, the examiner argued that:

"Fortina provides a supporting disclosure that teaches the detection of a common mutation with a target sequence utilizing primers that target the mutation (abstract; pg. 354, materials and methods, primer targeting ΔF508, for example). Fortina clearly shows that primers targeting a particular mutation aid in detecting the presence of such a mutation by allowing amplification of the target sequence.

It would have been prima facie case of obvious to a skilled artisan at the time of invention to design primers to target subfamily-specific mutations within human Alu sequences such that particular subfamily human Alu sequences are amplified since the prior art demonstrates such primers useful in such a capacity."

MPEP §2143.01 states that

"I. *PRIOR ART **>SUGGESTION OF< THE DESIRABILITY OF THE CLAIMED INVENTION

Obviousness can * be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006) (discussing rationale underlying the motivation-suggestion-teaching *>test< as a guard against using hindsight in an obviousness analysis)."

Here, the examiner merely showed that utilizing primers that target the mutations are useful so that it can be used in Sifis *et al.* in view of Palmirotta *et al.*, in further view of Jurka. This showing is not sufficient to show the suggestion of the desirability of the claimed invention.

Please note that the *primers* may be designed without including subfamily-specific diagnostic mutations in the primer sequences themselves, whereas the *amplified products* amplified by the primers are likely to include subfamily-specific diagnostic mutations. The examiner did not provide why the ordinary skilled person in the art would incorporate the subfamily-specific diagnostic mutations are incorporated into the primer sequences. The fact that it is useful is not sufficient to support obviousness.

The examiner failed to show the suggestion of the desirability of the claimed invention.

Furthermore, Fortina et al. teach away from the claimed invention because the 3' primer should not be mutant-specific. Fortina et al. is directed to multiplex allele-specific polymerase chain reaction, wherein only 5'-primers are mutant-specific and the 3' primer should be common. (See page 354.)

Also, there is no teaching, suggestion, or motivation to replace the primers of Sifis et al. in view of Palmirotta et al. Jurka which are not related to the multiplex PCR with the primers of Fortina specified for the multiplex PCR.

Therefore, there is no teaching, suggestion, or motivation to modify or combine the references, and the alleged combined prior art references teach away from the claimed invention.

B. Claim 5 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis *et al.* (J Forensic Sci. 2002 May; 47(3): 589-92) in view of Palmirotta *et al.* (Journal of Forensic Science. March 1998. (43) 2, 431-434), in further view of Jurka (Nucleic Acids Research. 1993. Vol. 21. No. 9, 2252), as evidenced by Batzer et al. (Journal of Molecular Evolution, 1996, 42, 3-6), and in further view of Buck *et al.* (BioTechniques. September 1999. 27: 528-536).

The examiner admitted that SEQ ID NOs:3 and 4 are not taught in Sifis et al. and Palmirotta et al, but are contained in Jurka.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish prima facie case obviousness. *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

1. The examiner's argument is at most that the references can be combined or modified. The examiner did not show the desirability of the combination.

First, the fact that the sequence is known does not mean that the DNA fragment is necessarily obvious.

The applicant invited the examiner's attention to consider the following reference, <http://www.jpo.go.jp/shiryou_e/toushin_e/kenkyukai_e/contents.htm>, particularly, <http://www.jpo.go.jp/shiryou_e/toushin_e/kenkyukai_e/uspto/u50.htm> which states that even if the whole sequence is disclosed, claims directed to a method of using Y' might be novel even for open ended claim language such as "a method of using a probe comprising Y'.

(1) In response to the applicant's arguments, the examiner stated that the examiner was unable to open the hyperlink and thus did not review the entire reference. The hyperlink is

working well. For the examiner's information, the entire reference is retrieved and attached hereto. Therefore, reconsideration is respectfully requested.

(2) The examiner also argued that "the examiner agrees that a method directed to the use of a probe molecule drawn to a larger known sequence, even for open ended claim language, might be novel. In this case, the Office has found these particular claims obvious in view of the available prior art

The examiner's reasoning is hardly understood. The examiner's reasoning was that since "the identical sequence ... is contained in the sequence provided by Jurka... Furthermore, the identical complement of the sequence ... is contained in the sequence provided by Jurka ...," the primers are obvious. That is, the examiner's reasoning is that since the sequences for the primers are contained in a certain larger known sequence, the primers are obvious over the known sequences. At the same time, the examiner admitted that the primers may be novel even if the sequences for the primers are contained in a certain larger known sequence.

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (CAFC, 2006).)

The examiner failed to establish a prima facie case of obviousness.

(3) With respect to Buck et al., the examiner's response is not proper for the following reasons.

(a) The examiner argued that Buck is relied upon to provide evidence of the equivalence of primers absent a secondary consideration.

The examiner's reasoning includes the replacement of the primers in Sifis et al. with the primers which can be allegedly obtained from the known sequence in Jurka et al.

MPEP §2144.06 expressly states "Art Recognized Equivalence for the Same Purpose". The purpose of Sifis et al. is to design more sensitive method for the quantitation of genomic DNA by Alu amplification. The purpose of Sifis et al. and what the examiner showed based on Buck et al. are not the same purpose.

It should be noted that Buck et al. is directed to a qualitative assay, whereas Sifis et al. are directed to a quantitative assay. Since Buck et al. is for a qualitative assay, Buck et al. acknowledged that different results may be obtained using less carefully purified DNA templates with unusual sequences or structures or in less rigorously controlled sequencing operations." (See page 535, last paragraph to page 536, first paragraph in Buck et al., emphasis added.) That is, Buck et al. admitted that the equivalence cannot be guaranteed in unusual sequences or structures or in less rigorously controlled sequencing operations. Accordingly, the teaching of Buck et al. can be applied only to the same reaction condition as described in Buck et al., and cannot be applied to the quantitation of human DNA in an unknown sample. The primers of

Sifis et al. are not solely for automated DNA sequencing of a 300-bp test sequence as disclosed in Buck et al. Accordingly, they are not for the same purpose.

Therefore, the art does not recognize equivalence for the same purpose.

For the foregoing reasons, claim 5 is not obvious over the prior art.

(b) Please also note that the examiner's reasoning can be rebutted by evidence.

MPEP §2145 states that:

"Office personnel should consider all rebuttal arguments and evidence presented by applicants. See, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687 (error not to consider evidence presented in the specification). *C.f., In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996) (error not to consider factual evidence submitted to counter a 35 U.S.C. 112 rejection); *In re Beattie*, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1042-43 (Fed. Cir. 1992) (Office personnel should consider declarations from those skilled in the art praising the claimed invention and opining that the art teaches away from the invention.); *Piasecki,* 745 F.2d at 1472, 223 USPQ at 788 ("[Rebuttal evidence] may relate to any of the *Graham* factors including the so-called secondary considerations.").

Rebuttal evidence may include evidence of "secondary considerations," such as "commercial success, long felt but unsolved needs, [and] failure of others." *Graham v. John Deere Co.*, 383 U.S. at 17, 148 USPQ at 467. See also, e.g., *In re Piasecki*, 745 F.2d 1468, 1473, 223 USPQ 785, 788 (Fed. Cir. 1984) (commercial success). Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art."

Here, the examiner should consider the applicant's rebuttal evidence stated in the specification.

"[0065] The inventors have also systematically tested each assay for human specificity, especially with regard to closely related non-human primates and in multiple diverse human genomes. In contrast, documentation associated with other currently available methods is vague with respect to the cross-hybridization/amplification of other closely related species. In addition, the range of quantitation using the combined intra-Alu based assays (Yb8 and Yd6 subfamilies) is approximately 10^5 based on the above described 10-fold dilution series experiments. By contrast, the current commercial quantitation systems such as AluQuant™ and Quantiblot™ have a 500-fold and 100-fold quantitation range, respectively. In other words, the low range detection limit of the intra-Yb8 assay described here exceeds the commercial systems by a minimum of 100-fold and it also exceeds the method recently reported by Sifis et al., supra, by at least 2.5-fold. Further, since Sifis et al., supra, do not address possible mammalian cross-amplification with their assay, the intra-Yb8 method reported here is even more sensitive for the identification of human DNA from complex sources." (Emphasis added.)

Even when the examiner properly establishes a prima facie case of obviousness, the examiner should consider the evidence stated in the specification for the examination of the patentability.

For the foregoing reasons, claim 5 is not obvious over the prior art.

C. Claim 9 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. in view of Palmirotta et al., in further view of Jurka as evidenced by Batzer et al. as applied to claim(s) 1, 7, 8, 21, and 22 above, and in further view of Gelmini et al. (Clinical Chemistry. 1997. 43:5, Pages 752-758).

Claim 9 depends from claim 1. Since claim 1 is patentable, claim 9 is also patentable.

No fee is incurred by this Amendment.

In view of the above, all claims are submitted to be allowable and this application is believed to be in condition to be passed to issue. Reconsideration of the rejections is requested. Should any questions remain unresolved, the Examiner is requested to telephone Applicant's attorney.

Respectfully submitted,

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Date: 7/7/2008
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